Atty Docket No: 12E-989110US
Client Ref: G67

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Jagdish Parasrampuria; Maxine B. Yonker; Kenneth E. Schwartz; Marc J. Gurwith

Examiner: Qazi, S.

Application No.: 09/526,802

Art Unit: 1616

Filed: 3/16/2000

For: **DHEA Composition And Method**

APPEAL BRIEF

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

APPEAL BRIEF

Real Party in Interest.

The real party in interest in the present appeal is Genelabs Technologies, Inc., the assignee of the above-referenced application.

Related Appeals and Interferences.

Appellants, Appellants' Attorney, and the assignee of the present application are unaware of any appeals or interferences that will directly affect, be directly affected by, or have a bearing on, the Board's decision in the present appeal.

Status of Claims.

On July 7, 2003, Appellants appealed from the final rejection of claims 1-10 and 36-39. Originally filed claims 11-35 were cancelled without prejudice pursuant to a restriction requirement. Claims 36-39 were added in an Amendment (dated May 7, 2002) filed response to the first Office Action. Appellants note that the Final Office Action (dated April 4, 2003) indicates, in

the Office Action Summary, that claim 9 is subject to restriction and/or election requirement. However, as Appellants pointed out earlier, in response to the second Office Action, the indication that claim 9 was withdrawn from consideration appears to be a typographical error. *See* Amendment dated December 16, 2002. Furthermore, the Final Office Action does not indicate that claim 9 is withdrawn from consideration and includes claim 9 among the rejected claims. *See* Final Office Action, page 2. Accordingly, Appellants believe that all pending claims (1-10 and 36-39) are under consideration.

Status of Amendments.

The claims were not amended in response to the second or Final Office Actions. Accordingly, the appealed claims are the claims as amended in the Amendment (dated May 7, 2002) filed response to the first Office Action.

Summary of Invention.

Appellants' invention provides a pharmaceutical formulation comprising dehydroepiandrosterone (DHEA), at least 85% of which is present as the form I polymorph, and at least one pharmaceutical excipient, as well as method for preparing such a formulation. As discussed in Appellants' specification, DHEA was known to occur in several different hydrate and crystal forms. *See* Appellants' specification, page 5, lines 7-30. The known anhydrate forms included forms I-V. Appellants discovered that conditions reported by others for enriching for the form I polymorph yielded formulations that are contaminated with a previously unknown form, which Appellants have termed "form VI." The contaminating form VI could not be detected using standard analytical techniques such as X-ray diffraction, infrared (IR) spectroscopy, or differential scanning calorimetry (DSC). Rather, ^{13}C-solid state NMR (^{13}C-SSNMR) analysis was required to detect the presence of form VI. To prepare truly pure form I (*i.e.*, substantially free of form VI), Appellants crystallized DHEA from 2-propanol, acetone, or acetonitrile and then carried out an additional crystallization step. Specifically, this step entailed "suspending the precipitate from the first step in ethyl acetate (about 100 mL/30 g of DHEA) and stirring the resulting slurry at room temperature for about one week, followed by filtration." Appellants' specification, page 5, lines 21-30. Appellants confirmed the purity of this preparation by ^{13}C-SSNMR analysis, a technique never previously employed to assess the purity of DHEA preparations.

The appealed claims are set forth in Appendix A.

Issues.

In the Final Office Action (dated April 4, 2003), claims 1-10 and 36-39 were rejected under 35 U.S.C. § 103(a) as unpatentable over Morales *et al.* (U.S.P.N. 5,407,927) and Loria *et al.* (U.S.P.N. 5,077,284) in combination with Chang *et al.* (DN 123:265915, HCAPLUS, abstract of J. Pharm. Sci. 84:1169-79 (1995)). This rejection was maintained in the Advisory Action (dated June 25, 2003).

Grouping of Claims.

Claims 1, 5, 9, 10, 36 and 38 stand or fall together; claims 2 and 6 stand or fall together; claims 3 and 7 stand or fall together; claims 4 and 8 stand or fall together; and claims 37 and 39 stand or fall together.

Argument.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate that (1) all elements of the invention are found in the cited art; (2) the cited art provided motivation to combine or, if necessary, modify these elements to arrive at the claimed invention; and (3) the cited art revealed that, in making the claimed invention, those of ordinary skill in the art would have a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

Of the pending claims, claims 1, 5, and 36-39 are independent. Claims 1, 36, and 37 relate to pharmaceutical formulations "comprising dehydroepiandrosterone (DHEA), at least 85% [or more] of which is present as the form I polymorph." Claims 5, 38, and 39 related to methods comprising "mixing at least one solid pharmaceutical excipient with dehydroepiandrosterone (DHEA), at least 85% [or more] of which is present as the form I polymorph." Thus, all of the pending claims require DHEA, which is at least 85% form I. Appellants respectfully submit that this element of the claims is not found in the cited references; the cited references provide no motivation to produce such formulations, and the cited references fail to provide a reasonable expectation that form I DHEA formulations of this purity could be obtained.

The Examiner relies on Morales and Loria as teaching "the formulation of DHEA for various methods of treatment" and cites "especially lines 37-62, col. 1; lines 4-10 and lines 59-66, col. 12 in US 5,077,284 and lines 59-68, col. 2; lines 25-58, col. 3 and table 2 in col. 7 in US 5,407,927." Second Office Action (dated June 14, 2002), page 3. Neither Morales nor Loria teach

or suggest anything about the DHEA form(s) present in the formulations disclosed in these references.

The Examiner contends that Chang teaches the recited form I DHEA formulations, noting:

> Chang et al. teaches solid state crystallization of DHEA and its polymorph [*sic*] (forms I-III). Furthermore, it discloses that form I is more stable than others.

Final Office Action, page 2.

Appellants respectfully point out that the claimed invention relates to formulations having ***at least 85%*** form I DHEA. So the proper focus of the obviousness inquiry is whether Chang teaches or suggests formulations having this high a concentration of form I. Moreover, it is also necessary to consider whether Chang teaches or suggests formulations having 90%, 95%, and 99% form I DHEA, as recited in dependent claims 2 and 6 (90%); 3, 7, 37, and 39 (95%); and 4 and 8 (99%).

The Examiner acknowledges that the claims relate to a specific polymorphic form of DHEA, but states:

> It would have been obvious to one skilled in the art at the time when instant invention was made, to be motivated to prepare additional beneficial preparations and formulations of DHEA by using any polymorphic form of this compound especially form I and would [*sic*] expect the same results because when the compositions of the compound would be prepared, it would be the same after dissolving in the solvent no matter what polymorphic form exists in the solid state.

Final Office Action, page 3. The Examiner's statement that the one "would expect the same results" because polymorphic form is irrelevant after dissolution misses the point that Appellants are claiming formulations containing different polymorphic forms of DHEA, not DHEA in solution. Under the Examiner's rationale, it would never be possible to patent a new polymorphic form of a known compound. Clearly, this is not the law. For example, in *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043 (Fed. Cir. 1995) (discussed in more detail below), the court upheld claims to "Form 2" rantidine hydrochloride.

More to the point is that Chang does not teach or suggest DHEA formulations that are at least 85% form I, much less how to achieve such formulations. In particular, Chang fails to present any convincing evidence that such a formulation was prepared. Chang discloses form I-

containing formulations, but merely assumes that these formulations were pure. *See* Chang, J. Pharm. Sci. 84:1169-79 (1995), page 1173, col. 2. As Appellants' specification points out, this assumption was incorrect. Chang was unaware of the likelihood that their form I preparation was contaminated with a heretofore unknown form, namely form VI. In particular, note the passage at page 5, lines 7-20 of Appellants' specification, which explains that Chang's method for producing form I actually produced a mixture of form I and form VI. To prepare truly pure form I, Appellants crystallized DHEA from 2-propanol, acetone, or acetonitrile, as described by Chang, and then carried out an additional step. Specifically, this step entailed "suspending the precipitate from the first step in ethyl acetate (about 100 mL/30 g of DHEA) and stirring the resulting slurry at room temperature for about one week, followed by filtration." Appellants confirmed the purity of this preparation by ^{13}C-SSNMR analysis, a technique not employed by Chang.

Chang performed studies in which different formulations were mixed and then measured using X-ray powder diffraction. Chang, page 1173-1174. Chang concluded from these studies that: "These results indicate that the purities of forms I-III and S1 are as high as 95%, and X-ray powder diffraction can ***potentially*** be employed as a method of estimating the purity of polymorphs of DHEA." Chang, page 1175, col. 1 (emphasis added). Appellants point out that these results were obtained using an analytical method that was unable to distinguish form I from form VI. As Appellants have demonstrated, ^{13}C-SSNMR is the only analytical method known to be capable of this distinction. Because Chang did not use ^{13}C-SSNMR, Chang's conclusions regarding the purity of their form I preparation are not scientifically credible. One skilled in the art would therefore discount Chang's claim to have prepared a 95% form I DHEA formulation. Accordingly, Appellants submit that Chang fails to teach or suggest formulations having ***at least 85%*** form I DHEA.

In support of this point, Applicants submitted the Declaration of Dr. Patrick Stahly, the Chief Operating Officer and Vice President of Research and Development for SSCI, Inc. (A copy of the Stahly Declaration is attached.) SSCI is a contract research laboratory specializing in crystallization, characterization, and chemistry of solids, and Dr. Stahly is an expert in the field of crystallization and polymorphism, as evidenced by his Curriculum Vitae.

Dr. Stahly was asked to comment on whether a person of ordinary skill in the art of the preparation and characterization of different polymorphic forms of compounds would interpret Chang as describing DHEA preparations containing at least 85% form I DHEA. Dr. Stahly's conclusion, based on actual experimental data, which accompany the declaration, is that a person of

ordinary skill in this field would not view Chang as describing such preparations. Stahly Declaration, para. 10. In arriving at this conclusion, Dr. Stahly makes the following points:

1. "[S]tandard crystallization of DHEA out of organic solutions, such as Chang described, can yield mixtures of form I DHEA with significant amounts (*e.g.*, 30-40%) of form VI DHEA." Stahly Declaration, para. 4.

2. "None of the analytical techniques used by Chang to characterize the DHEA polymorph preparations can distinguish between form I DHEA and form VI DHEA." Stahly Declaration, para. 5. In support of this point, Dr. Stahly notes that Chang erroneously believed that X-ray powder diffraction could be used to estimate the purity of DHEA polymorphs. *Id.* at para. 6. However, Dr. Stahly demonstrates that "a mixture of form I and form VI DHEA exhibit essentially the same X-ray powder diffraction pattern as a pure form I preparation." *Id.* at para. 8.

3. "As described in the present application, solid state, carbon-13 NMR, a technique that Chang did not use, can distinguish between a pure form I DHEA preparation, a mixture of forms I and VI, and a pure form VI DHEA preparation." Stahly Declaration, para. 9. Using this technique, Dr. Stahly analyzed the form I:VI mixture and pure form I preparations which where indistinguishable by X-ray powder diffraction. *Id.* The results indicate that the form I:VI mixture contains on the order of 30-40% form VI DHEA (*i.e.*, at most, 60-70% form I DHEA), which was undetectable using X-ray diffraction. *Id.* at para. 10.

4. Thus, the results "establish that Chang's form I preparations could have contained as much as 40% form VI." Stahly Declaration, para. 10.

Dr. Stahly's Declaration demonstrates that Chang's form I DHEA formulations are not necessarily "at least 85% form I." M.P.E.P. § 2112.02 states that a "prima facie case can be rebutted by evidence showing that the prior art products do not ***necessarily*** possess the characteristics of the claimed product." M.P.E.P. § 2112.02 (citing *In re Best*, 562 F.2d 1252, 1255 (C.C.P.A. 1977). Thus, even assuming *arguendo* that Chang supported a *prima facie* case of obviousness, the Stahly Declaration is sufficient to rebut it. In this regard, *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043 (Fed. Cir. 1995) is instructive. In this case, the court upheld claims to "Form 2" rantidine hydrochloride crystals based on conflicting evidence regarding the form produced in a prior-art process. The alleged infringer, Glaxo, presented evidence that the prior-art process produced Form 2 each of the 13 times its experts performed the process, whereas the patentee, Novopharm, presented evidence that only Form 1 was produced. *Id.* at 1047. The district court determined that the process could

produce either form and therefore found that Glaxo had failed to establish that the prior-art process inherently produced Form 2. The Federal Circuit held that the "district court correctly rejected Glaxo's anticipation defense." *Id.*

The Board of Patent Appeals and Interferences has also followed the rule that the presence of a claimed characteristic in a prior-art product may not be established based on possibilities. In *Ex Parte Levy*, 17 USPQ2d 1461 (Bd. Pat. App. Inter. 1990), for example, the Board reversed a 35 U.S.C. § 102 rejection of claims reciting a biaxially oriented polymeric balloon because the evidence of record regarding this feature was in conflict. The Board stated:

> According to the membrane equation calculations reported in Levy's declaration . . . , Schjeldahl's balloon could not possibly exhibit the tensile characteristics of a biaxially oriented balloon. Levy's calculations are inconsistent with those of Pinchuk . . . . suffice it to say, ***the conflicting calculations taint that factual determination of inherency with impermissible conjecture.***

Ex parte Levy, at 1464 (emphasis added).

Appellants submit that any contention that Chang's DHEA preparations contained at least 85% form I DHEA is similarly tainted by impermissible conjecture, especially in light of the Stahly Declaration. Thus, a *prima facie* case of obviousness either has not been established or, if established, has been rebutted by Appellants' demonstration that an element of the invention (at least 85% form I DHEA) cannot definitively be found in the cited references.

In addition to failing to satisfy the first requirement for a *prima facie* case of obviousness, the record is deficient with respect to the second and third requirements for a *prima facie* case. Specifically, because Chang was unaware of the existence of contaminating form VI, Chang provides no motivation for removing contaminating form VI to achieve the high-purity formulations recited in the pending claims. In the Final Office Action, the Examiner states: "Motivation is to prepare formulations, of DHEA form I polymorph [*sic*] because form I is taught to be more stable . . . ." Final Office Action, page 3. This statement addresses the motivation for selecting form I for pharmaceutical formulations, but not the motivation that would lead one skilled in the art to the claimed invention, which is characterized by at least 85% form I DHEA.

It is well-settled that a *prima facie* case requires ***specific*** motivation to produce the invention. The Federal Circuit emphasized the necessity for finding specific motivation in *In re Rouffet*, 149 F.3d 1350 (Fed. Cir. 1998). There, the court stated:

> "[V]irtually all [inventions] are combinations of old elements." *Environmental Designs, Ltd. v. Union Oil Co., 713 F.2d 693, 698, 218 U.S.P.Q. 865, 870 (Fed. Cir. 1983)*; *see also Richdel, Inc. v. Sunspool Corp., 714 F.2d 1573, 1579-80, 219 U.S. P.Q. 8, 12 (Fed. Cir. 1983)* ("Most, if not all, inventions are combinations and mostly of old elements."). Therefore an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would be "an illogical and inappropriate process by which to determine patentability." *Sensonics, Inc. v. Aerosonic Corp., 81 F.3d 1566, 1570, 38 U.S.P.Q. 2d 1551, 1554 (Fed. Cir. 1996).*

Id. at 1357. The court then noted that the Board had failed to "explain what ***specific*** understanding or technological principle within the knowledge of one of ordinary skill in the art would have suggested" the invention. *Id.* (emphasis added). In *In Re Werner Kotzab*, 217 F.3d 1365 (Fed. Cir. 2000), the Federal Circuit reiterated that:

> [A] rejection cannot be predicated on the mere identification in . . . [the cited reference] of individual components of claimed limitations. Rather, ***particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.***

In re Kotzab, at 1369-1372 (emphasis added).

Applying the requirement for specific motivation to the present case, the Examiner must make particular findings as to the reason one skilled in the art would further purify a DHEA preparation "assumed to be pure." *See* Chang, page 1173, col. 2. The claimed formulations must be at least 85% form I DHEA, which means no more than 15% form VI DHEA. It is undisputed that none of the cited references teaches or suggests that form VI is a substantial contaminant of form I preparations. The record is therefore necessarily devoid of any motivation for substantially removing form VI DHEA. The notion that one could be motivated to remove a contaminant that one does not know is present simply defies logic.

The Examiner may contend that some form of generic motivation exists to further purify a compound intended for pharmaceutical use. Appellants respectfully submit that such generic motivation fails to satisfy the second requirement for a *prima facie* case. In particular, the

required motivation must lead one skilled in the art to the claimed invention. A generic motivation to further purify a compound could arguably lead one skilled in the art to remove known contaminants, but not unknown contaminants. Because the existence of form VI DHEA was unknown, as was its tendency to co-crystallize with form I DHEA, there could be no motivation to produce form I DHEA formulations having no more than 15% form VI (*i.e.*, at least 85% form I), much less formulations having no more than 10%, 5%, or 1% form VI (*i.e.*, at least 90%, 95%, and 99% form I). Accordingly, Appellants submit that the cited art provides insufficient motivation to arrive at the claimed invention and thus fails to satisfy the second requirement for a *prima facie* case of obviousness.

With respect to the third requirement for a *prima facie* case, Chang fails to provide any guidance as to how to reliably produce form I DHEA free of substantial (*e.g.*, greater than 15%) form VI, and therefore no reasonable expectation that this result could be achieved. Similarly, the record is devoid of any basis for supposing that formulations having no more than 10%, 5%, or 1% form VI (*i.e.*, at least 90%, 95%, and 99% form I) could be produced. The Examiner has not even addressed this requirement for a *prima facie* case.

In summary, this record does not support the conclusion that all elements of the invention are found in the cited art. The motivation cited by the Examiner would not lead one skilled in the art to the claimed invention. And the cited art does not reveal that, in making the claimed invention, those of ordinary skill in the art would have a reasonable expectation of success. As none of the requirements for a *prima facie* case of obviousness has been satisfied, the § 103 rejection must be reversed, and such reversal is respectfully requested.

In justifying the rejection, the Examiner states that "[d]ifferent polymorphic forms are not patentable over each other in the absence of unexpected properties." Final Office Action, page 3. The Examiner has consistently maintained this position, but has not cited any authority to support it. Appellants can find no authority that justifies the application of such a *per se* rule. To the contrary, Appellants respectfully point out that the Court of Appeals for the Federal Circuit has, in no uncertain terms, stated that the application of *per se* rules to a determination of obviousness contravenes § 103: "section 103 requires a fact-intensive comparison of the claimed process with the prior art rather than the mechanical application of one or another *per se* rule." *In re Ochiai*, 71 F.3d 1565, 1571 (Fed. Cir. 1995) (citations omitted). The court continued:

> The use of *per se* rules, while undoubtedly less laborious than a searching comparison of the claimed invention--including all its limitations--with the teachings of the prior art, flouts section 103 and the fundamental case law applying it. *Per se* rules that eliminate the need for fact-specific analysis of claims and prior art may be administratively convenient for PTO examiners and the Board. Indeed, they have been sanctioned by the Board as well. But ***reliance on per se rules of obviousness is legally incorrect and must cease.*** Any such administrative convenience is simply inconsistent with section 103, which, according to *Graham* and its progeny, entitles an applicant to issuance of an otherwise proper patent unless the PTO establishes that the invention *as claimed* in the application is obvious over cited prior art, based on the specific comparison of that prior art with claim limitations. We once again hold today that our precedents do not establish any *per se* rules of obviousness, just as those precedents themselves expressly declined to create such rules.

Id. at 1572 (emphasis added).

Furthermore, Appellants' claims are directed to a formulation having a particular polymorphic form ***at a specific concentration***. Therefore, the question the Examiner must address is whether Chang would lead one skilled in the art to produce formulations containing at least 85%, 90%, 95%, or 99% form I DHEA. Appellants respectfully submit that Chang provides no credible basis for the contention that one skilled in the art, following Chang, could produce such formulations. To the contrary, Appellants found that form I DHEA formulations are typically contaminated with significant levels of form VI DHEA and that Chang's studies could not distinguish between DHEA formulations containing significant amounts (*i.e.*, greater than 15%) of form VI mixed with form I and substantially pure (*i.e.*, 85% or greater) form I formulations. Furthermore, because Chang *et al.* were not aware of the existence of form VI DHEA, the Chang article necessarily fails to enable the reproducible production of formulations containing at least 85% form I (*i.e.*, no more that 15% form VI) from form I:form VI mixtures, much less the production of formulations containing at least 90%, 95%, or 99% form I.

The only statement in the Final Office Action that addresses the purity element in the recited claims is that "[i]t had been held that . . . changing the form, purity or other characteristics of an old product does not render the novel form patentable ***where the difference in form, purity or characteristic was inherent in or rendered obvious by the prior art.***" Final Office Action, page 3 (citing *In re Cofer*, 354 F.2d 664 (C.C.P.A. 1966) (emphasis added). The Examiner appears to believe that this rule of law dictates that a higher purity form of an old product is *per se*

unpatentable. However, the Federal Circuit has stated that *per se* analysis of obviousness "is founded on legal error because it substituted supposed *per se* rules for the particularized inquiry required by section 103." *In re Ochiai*, 71 F.3d 1565, 1571 (Fed. Cir. 1995) According to the court, this analysis "necessarily produces erroneous results." *Id.* Moreover, the Examiner's interpretation of *Cofer* overlooks the condition that "the difference in form, purity or characteristic was inherent in or rendered obvious by the prior art." Appellants submit that Chang manifestly fails to satisfy this condition and therefore that the Examiner's reliance on *Cofer* is misplaced.

In fact, a careful reading of *Cofer* indicates that this decision supports Appellants' position, rather than the Examiner's. The claims at issue in *Cofer* related to a compound termed 2,2-B in a novel form, namely as free-flowing crystals. As the court noted:

> According to appellant's specification no method has yet been described which permits production of pure 2,2-B directly by the reaction of epichlorohydrin with "Bisphenol A." Prior attempts to recover 2,2-B have resulted only in recovery of a relatively viscous liquid containing impurities which adversely affected the usefulness of epoxy resins prepared therefrom.

Cofer, 354 F.2d at 665. The Examiner in *Cofer* had rejected the claims as obvious under 35 U.S.C. § 103 over references disclosing the viscous form of 2,2-B, and the Board of Patent Appeals and Interferences had affirmed this rejection. *Id.* at 665-66.

The court framed the issue in *Cofer* as follows:

> The basis for the rejection is, essentially, that the claimed product is merely a different form of a known compound, and, notwithstanding that some desirable results are obtained therefrom, since the product has the same utility as the art compound, the claimed product is deemed to be unpatentable thereover.

Id. at 666. The Examiner had argued that the difference in properties resulted only from a greater degree of purity and was therefore to be expected. *See id.* at 667. Appellants submit that the facts of *Cofer* are analogous to those of the present application. Specifically, in both cases, the claims were rejected as obvious over art disclosing a less pure form of the same material. In *Cofer*, the Board regarded the fact that the claimed product had the same utility as the prior-art product as dispositive of obviousness. In the present case, the Examiner takes the position that the form I DHEA in Appellants' composition has the same properties as the form I DHEA described by Chang and that this necessitates a finding of obviousness.

However, the *Cofer* court indicated that such considerations are not dispositive, stating:

> We think the board failed to address itself to other factors which must be given weight in determining whether the subject matter as a whole would have been obvious, namely, ***whether the prior art suggests the particular structure or form of the compound or composition as well as suitable methods of obtaining that structure or form***. The new form of the compound set forth in the claims is as much a part of the "subject matter as a whole" to be compared with the prior art as are other properties of the material which make it useful.

Cofer, 354 F.2d at 668 (emphasis added). Accordingly, the court reversed the rejection, concluding that "the record fails to support a holding that those skilled in the art should have known that 2,2-B would exist in crystalline form or that it would be known how to obtain such crystal." *Id.* The same rationale dictates that the § 103 rejection be withdrawn in the present case. That is, the record fails to support a conclusion that those skilled in the art would have known, prior to Appellants' invention, that DHEA formulations wherein at least 85% of the DHEA present was form I could be produced or how to produce them.

In a later case, *In re Irani*, 166 USPQ 24 (C.C.P.A. 1970), the C.C.P.A. used the same rationale in reversing a § 103 rejection of a claim to a crystalline anhydrous ATMP. *Id.* at 25. The references cited in the § 103 rejection disclosed "glassy" (non-crystalline) ATMP. *Id.* The court explained the basis for the rejection as follows:

> The examiner was of the opinion that one skilled in the art knowing of Petrov's "glassy solid" form of ATMP would be motivated to attempt the preparation of crystalline anhydrous ATMP by the knowledge that some amino phosphonic acids exist in crystalline form (Kosolapoff and Bersworth) and that some amino phosphonic acids are useful as softeners, sequesterants, or chelating agents (Pikl and Bersworth).

Id. However, the court found that "even assuming that one skilled in the art could have predicted with reasonable certainty that crystalline anhydrous ATMP could be produced, we are not convinced on this record that it would also have been obvious *how* this could be achieved." *Id.*; *see also In re Seaborg*, 328 F.2d 996 (C.C.P.C. 1963) reversing a § 103 rejection in part because the prior-art reference did not allow one to "specify with any certainty the exact procedures which could be followed, without the exercise of more than the ordinary skill of the art" to produce the claimed invention.).

The facts of *Irani* are analogous to the facts of the present case. First, one skilled in the art could not have predicted with reasonable certainty that high-purity (85% or higher) form I DHEA formulations could be produced because none of the cited references provides a reliable means of even measuring the purity of form I DHEA formulations. Second, even if it were reasonable to suppose that such high-purity form I DHEA formulations could be produced, the record is devoid of any indication of how this may be achieved. Specifically, the record neither teaches nor suggests any means of removing contaminating form VI from form I DHEA formulations.

Also instructive is *In re Williams*, 171 F.2d 319 (C.C.P.A. 1948). At issue in this case was the patentability of a composition of the laevo rotary form of a compound "substantially free from the dextro rotary form" over prior-art references that included the Monatschefte reference. The latter disclosed the production of a compound having a formula identical to that recited in the claims. An article published after the relevant priority date established that the Monatschefte product was actually a racemic mixture of the laevo and dextro forms. The court stated that the "existence of a compound as an ingredient of another substance does not negative novelty in a claim to the pure compound." *Id.* The court then went on the analyze the issue of obviousness as follows:

> The rejection of the appealed claim on the ground of lack of invention was based on the theory that the Monatschefte publications disclose a racemic mixture which includes the laevo rotary form claimed by appellant, and that the procedure by which such a racemic mixture may be broken down into its dextro and laevo rotary components, was known to those skilled in the art. ***That rejection presupposes that the Monatschefte compound was known to be racemic since, if this were not the case, the idea of resolving it into components, to produce a laevo rotary compound, would not occur to one skilled in the art.*** Accordingly, unless it can be shown that the Monatschefte product was actually known to be racemic, prior to appellant's original filing date, or unless it would have been obvious to one skilled in the art that the product was, in fact, racemic, the rejection on the ground of lack of invention cannot be sustained.

Id. (emphasis added). Thus, the C.C.P.A. reversed a § 103 rejection based on facts that are substantially similar to those in the present case. Specifically, before the priority date of the present application, it was not known that form I DHEA preparations produced by standard crystallization of DHEA out of organic solutions, such as Chang described, can yield mixtures of form I DHEA with significant amounts (*e.g.*, 30-40%) of form VI DHEA. Nor was this problem obvious to one skilled

in the art at that time. Thus, as in the *Williams* case, Appellants have solved a problem that was previously unrecognized, namely how to separate a desired compound from a previously unknown contaminant. Just as in *Williams*, the idea of performing this separation would not have occurred to one skilled in the art prior to Appellants' invention. Therefore, in view of *Williams*, the obviousness rejection in the present case cannot be sustained.

In summary, Appellants submit that, when properly applied to the facts of the present case, the relevant authority (including that cited by the Examiner) leads to the conclusion that the pending claims are patentable over the cited references. Of the cited references, Chang is the only one that discusses form I DHEA. However, Chang's purity estimates are not scientifically credible because of the likelihood that Chang's formulations were contaminated with a significant amount of form VI DHEA. Moreover, Chang provides no hint as to how to obtain high-purity form I formulations free of form VI. Therefore, Chang, taken alone or with the other cited references, fails to teach or suggest formulations having at least 85% form I DHEA. Chang provides no motivation to remove form VI DHEA from form I DHEA to yield high-purity form I formulations because Chang was unaware of the existence of form VI. Chang therefore necessarily fails to provide a reasonable expectation that such high-purity form I DHEA formulations could be achieved. Because none of the requirements of a *prima facie* case have been met, Appellants respectfully request withdrawal of the § 103 rejection.

Conclusion

Appellants submit that the Examiner's rejection of claims 1-10 and 36-39 is improper, and withdrawal of this rejection by the Examiner or reversal of this rejection by the Board is respectfully requested.

The Commissioner is authorized to charge the fee under 37 C.F.R. § 1.17(c) and any other required fees, or to credit any overpayments, to Deposit Account No. 50-0893. This paper is submitted in triplicate.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 769-3509.

QUINE INTELLECTUAL PROPERTY LAW GROUP, P.C.
P.O. BOX 458
Alameda, CA 94501
Tel: 510 337-7871
Fax: 510 337-7877

Respectfully submitted,

Emily M. Haliday
Reg. No: 38,903

Attachments:

(1) Appendix A – Appealed Claims for 09/526,802

(2) Declaration of Dr. Patrick Stahly (including Exhibits A-J); and

(3) Curriculum Vitae of Dr. Patrick Stahly.

APPENDIX A

APPEALED CLAIMS FOR 09/526,802

1. A pharmaceutical formulation comprising dehydroepiandrosterone (DHEA), at least 85% of which is present as the form I polymorph, and at least one pharmaceutical excipient.

2. The formulation of claim 1, wherein at least 90% of said dehydroepiandrosterone (DHEA) is present as the form I polymorph.

3. The formulation of claim 1, wherein at least 95% of said dehydroepiandrosterone (DHEA) is present as the form I polymorph.

4. The formulation of claim 1, wherein at least 99% of said dehydroepiandrosterone (DHEA) is present as the form I polymorph.

5. A method for preparing a solid DHEA formulation, said method comprising:

mixing at least one solid pharmaceutical excipient with dehydroepiandrosterone (DHEA), at least 85% of which is present as the form I polymorph.

6. The method of claim 5, wherein at least 90% of said dehydroepiandrosterone (DHEA) is present as the form I polymorph.

7. The method of claim 5, wherein at least 95% of said dehydroepiandrosterone (DHEA) is present as the form I polymorph.

8. The method of claim 5, wherein at least 99% of said dehydroepiandrosterone (DHEA) is present as the form I polymorph.

9. The method of claim 5, further comprising the step of placing the solid formulation into a capsular container suitable for delivery to the gastrointestinal tract.

10. The method of claim 5, further comprising the step of compressing the solid formulation to form a tablet.

36. A pharmaceutical formulation comprising dehydroepiandrosterone (DHEA), at least 85% of which is present as the form I polymorph as determinable by solid state 13C NMR spectroscopy, and at least one pharmaceutical excipient.

37. A pharmaceutical formulation comprising dehydroepiandrosterone (DHEA), greater than 95% of which is present as the form I polymorph as determinable by solid state 13C NMR spectroscopy, and at least one pharmaceutical excipient.

38. A method for preparing a solid DHEA formulation, said method comprising:

mixing at least one solid pharmaceutical excipient with dehydroepiandrosterone (DHEA), at least 85% of which is present as the form I polymorph as determinable by solid state 13C NMR spectroscopy.

39. A method for preparing a solid DHEA formulation, said method comprising:

mixing at least one solid pharmaceutical excipient with dehydroepiandrosterone (DHEA), greater than 95% of which is present as the form I polymorph as determinable by solid state 13C NMR spectroscopy.

I hereby certify that this correspondence is being deposited with the United States Postal Service first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on March 7, 2003
QUINE INTELLECTUAL PROPERTY LAW GROUP, P.C.
By: Tracie Brooks

COPY

Atty Docket No: 12E-989110US
Client Ref: G67

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Jagdish Parasrampuria; Maxine B. Yonker; Kenneth E. Schwartz; Marc J. Gurwith
Application No.: 09/526,802

Filed: 3/16/2000

For: **DHEA Composition And Method**

Examiner: Qazi, S.

Art Unit: 1616

DECLARATION UNDER 37 C.F.R. 1.132

DECLARATION OF DR. PATRICK STAHLY

1. I, Dr. Patrick Stahly, am the Chief Operating Officer and Vice President of Research and Development for SSCI, Inc. SSCI is a contract research laboratory specializing in crystallization, characterization, and chemistry of solids. Our expertise includes polymorph screening, salt selection, analytical characterization of active pharmaceutical ingredients and dosage forms, quantitative mixture analysis, problem solving, optimization of crystallization processes, and educational short courses.

2. I have read the above-referenced patent application, including the currently pending claims, the Office Actions dated February 12, 2002 and June 14, 2002, and Chang *et al.*, J. Pharm. Sci. 84:1169-1179 (1995) (the Chang article), which is cited therein. I have been asked to comment on whether a person of ordinary skill in the art of the preparation and characterization of different polymorphic forms of compounds would interpret Chang as describing dehydroepiandrosterone (DHEA) preparations containing at least 85% form I DHEA.

3. I believe I am well qualified to address these questions, as I have devoted more than 25 years to the study of organic chemistry, including approximately 10 years studying crystallization and polymorphism. I received a Ph.D. in 1979 from the University of Maryland and immediately joined the Ethyl (later Albemarle) Corporation, where I worked for 15 years and attained the title of Senior Research Advisor. In 1995 I moved to SSCI as the Vice President of

Research and Development, acquiring the additional title of Chief Operating Officer in 1997. Thus, I have extensive, first-hand experience with the techniques relevant to the preparation and characterization of DHEA polymorphs.

4. Chang reported the characterization of the following solid forms of DHEA: three polymorphs (forms I-III), two monohydrates (forms S2 and S3), a 4:1 hydrate (form S1), and a methanol half-solvate (form S4). She also reported the observance of, but not characterization of, a form designated form V. Chang stated that crystals of "form I DHEA were prepared by dissolving excess DHEA in ethyl acetate, acetone, acetonitrile or 2-propanol with the aid of heat." Chang, page 1169, col. 2. Based on my experience, standard crystallization of DHEA out of organic solutions, such as Chang described, can yield mixtures of form I DHEA with significant amounts (*e.g.*, 30-40%) of form VI DHEA.

5. None of the analytical techniques used by Chang to characterize the DHEA polymorph preparations can distinguish between form I DHEA and form VI DHEA. Chang characterized the DHEA forms she produced using differential scanning calorimetry (DSC), thermogravimetry (TG), hot stage microscopy, X-ray powder diffractometry, Fourier transform infrared (IR) spectrometry, and Karl Fischer titration. Solution calorimetry and intrinsic dissolution rates were used to determine relative stabilities of the forms. Chang concluded that "[d]efinitive polymorph identification was based on X-ray powder diffraction patterns," and that "the purities of forms I-III and S1 are as high as 95%, and X-ray powder diffraction can potentially be employed as a method of estimating the purity of polymorphs of DHEA." These conclusions are based on data obtained from samples of the forms obtained by Chang and assumed to be pure. By comparison of the X-ray powder diffraction patterns of the samples obtained, Chang was able to recognize peaks unique to each sample, and was able to use these unique peaks to determine the purity of form I samples *only relative to the other forms known to Chang, namely forms II, III, and S1.* In fact, Chang noted that X-ray powder diffraction cannot always be used to determine purity due to peak overlap; for example, Chang stated that "forms S3 and S4 are indistinguishable...[by their] X-ray powder diffraction pattern[s]."

6. Chang erroneously believed that X-ray powder diffraction could distinguish all the DHEA polymorphs (with the possible exception of S3 and S4) and therefore used this technique to estimate the purity of DHEA polymorph preparations. Chang, page 1173, col. 2. More specifically, Chang determined the characteristic X-ray powder diffraction peaks for each of the

polymorph preparations. *Id.* Chang then performed mixing studies and determined that it was possible to detect "characteristic X-ray powder diffraction peaks of small amounts (5-10%) of a contaminating" form mixed with another form. *Id.* Based on these studies, Chang concluded that "the purities of forms I-III and S1 are as high as 95%, and X-ray powder diffraction can potentially be employed as a method of estimating the purity of polymorphs of DHEA." Chang, page 1175, col. 1. However, this conclusion rested on the assumption that Chang's preparations of forms I-III and form S1 were pure. Chang, page 1173, col. 2.

7. As a result of the work described in the present patent application, we now know that Chang's assumption was unjustified. That is, we now know that standard crystallization out of organic solvents can produce preparations containing a significant amount of form VI DHEA, in addition to form I DHEA. Further, the X-ray powder diffraction patterns of forms I and VI DHEA are so similar that mixtures of forms I and VI exhibit X-ray powder diffraction patterns indistinguishable from that exhibited by pure form I, a situation analogous to that reported by Chang for forms S3 and S4. As described in the patent application, solid state NMR, a technique not employed by Chang, was employed to distinguish form I DHEA from the previously unknown form VI DHEA. Application No. 09/526,802, page 7, lines 23-24.

8. To illustrate that a mixture of form I and form VI DHEA exhibit essentially the same X-ray powder diffraction pattern as a pure form I preparation, X-ray powder diffraction patterns of a form I:form VI mixture and pure form I are attached as Exhibits A and B. I estimate, based on the NMR spectra (described below), that the mixture contained as much as 30-40% form VI. Any comparison of X-ray powder diffraction patterns must always take into account the effect of "preferred orientation," which is the tendency of crystals to pack against each other with some degree of order as material is prepared for analysis. Preferred orientation leads to changes in relative peak intensities in X-ray powder diffraction patterns. The effect of preferred orientation is evident by comparing the X-ray powder diffraction pattern of a pure form I preparation (Exhibit B) to the X-ray powder diffraction pattern calculated from single crystal X-ray analysis data (Exhibit C). Note, for example, that a doublet is evident at about 20 °2θ in the former (Exhibit B) but the calculated pattern (Exhibit C), which does not exhibit preferred orientation effects, has only a single peak in this region because of the decreased intensity of the low-angle peak of the doublet. Unless the X-ray powder diffraction pattern of each pure form that may be present in a mixture is known, preferred orientation makes it difficult to determine if patterns exhibited by specific preparations represent

mixtures or not. The reason that the patterns of mixtures of forms I and VI and pure form I appear essentially the same is clear when one considers the X-ray powder diffraction pattern of a pure form VI preparation, which is attached as Exhibit D. Each of the significant peaks in the form VI preparation underlies a significant peak in the form I preparation. Chang indicates that the characteristic peaks for form I, in units of °2θ, are observed at 14.99°, 15.40, 17.68°, 18.05°, and 18.59. Chang, page 1173, col. 1. Exhibit D, the X-ray powder diffraction pattern for a pure form VI preparation, shows that the largest peaks observed for form VI coincide with the first four of Chang's characteristic form I peaks, and that essentially every peak in the form VI pattern occurs in regions where the form I pattern also contains peaks. Thus, X-ray powder diffraction cannot differentiate between mixtures of forms I and VI DHEA and pure form I DHEA.

9. As described in the present application, solid state, carbon-13 NMR, a technique that Chang did not use, can distinguish between a pure form I DHEA preparation, a mixture of forms I and VI, and a pure form VI DHEA preparation. The NMR spectra for each of the preparations discussed in the above paragraph are attached as Exhibits E-J. Only those portions of the specta where forms I and VI can be differentiated are shown. The chemical shift assignments are as follows:

Form	C18 (ppm)	C6 (ppm)
I	14.8, 14.1*	120.4, 118.9*
VI	14.4	118.5

* Form I is known to have two crystallographically independent molecules in the structure.

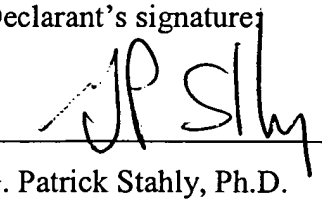
Exhibits E and F show the spectra for the form I:form VI mixture. All the peaks in the diagnostic regions are of approximately the same size. Since two peaks of each set of three result from form I, which has two crystallographically independent molecules in the structure, the ratio of the peak sizes is approximately 1:2 (form VI:form I), which is thus the ratio of the forms in the mixture. Based on this analysis, I estimate that this mixture contained approximately 30-40% form VI DHEA. This estimate assumes the NMR responses of the two forms are the same. Exhibit E shows three characteristic peaks, two (14.767 and 14.160 ppm) that are attributable to form I and one (14.403 ppm) that is attributable to form VI. Similarly, Exhibit F shows three characteristic peaks, two form

I peaks (120.352 and 118.896 ppm) and one form VI peak (118.532 ppm). Exhibits G and H are the spectra for the pure form I preparation, each of which show the two characteristic form I peaks. Exhibits I and J are the spectra for the pure form VI preparation, and these show the characteristic form VI peaks.

10. The results shown in the exhibits demonstrate that form VI present in form I DHEA preparations at levels as high as 30-40% cannot be detected by X-ray powder diffraction. Since form VI was unknown to Chang, she did not know what diagnostic analytical indicators to look for in her form I preparations that might indicate the presence of form VI. Chang's X-ray powder diffraction results do not support the conclusion that Chang's form I preparation was 95% pure. To the contrary, the results shown in the exhibits establish that Chang's form I preparations could have contained as much as 40% form VI. For this reason, it is my opinion that a person of ordinary skill in the art of the preparation and characterization of different polymorphic forms of compounds would not view Chang as describing DHEA preparations containing at least 85% form I DHEA.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Declarant's signature:



G. Patrick Stahly, Ph.D.

2/27/03

Date

EXHIBIT A

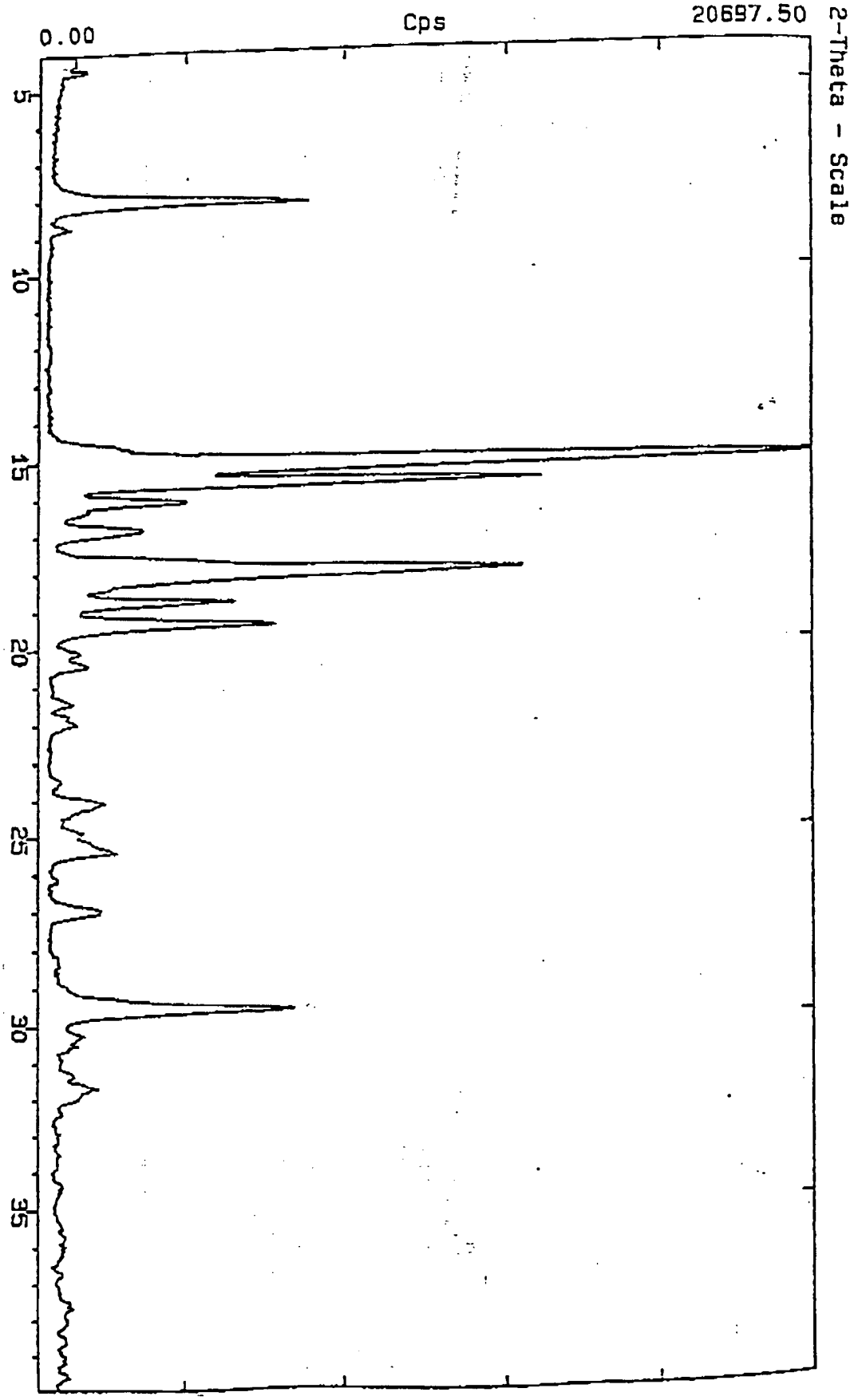


EXHIBIT B

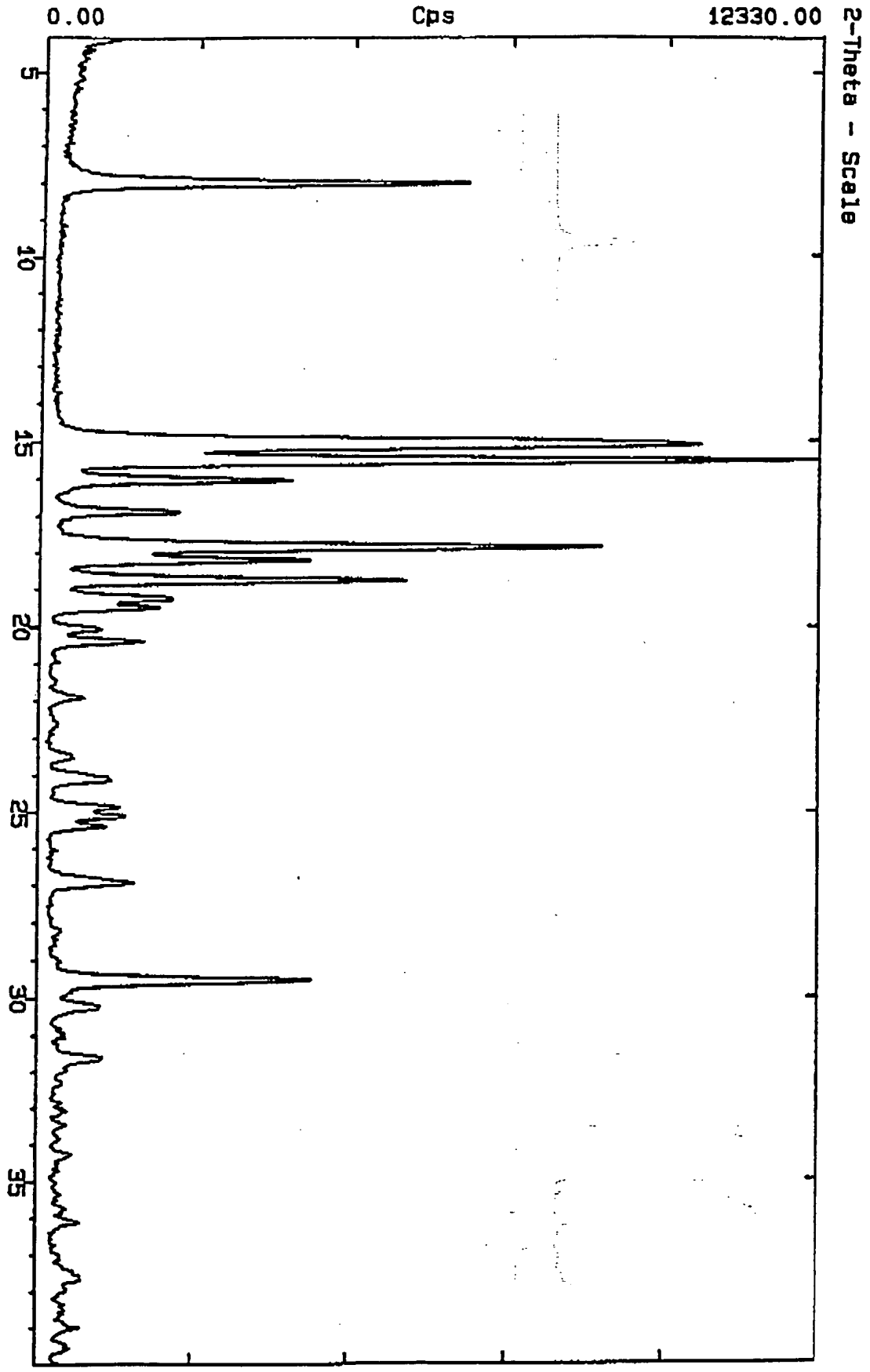
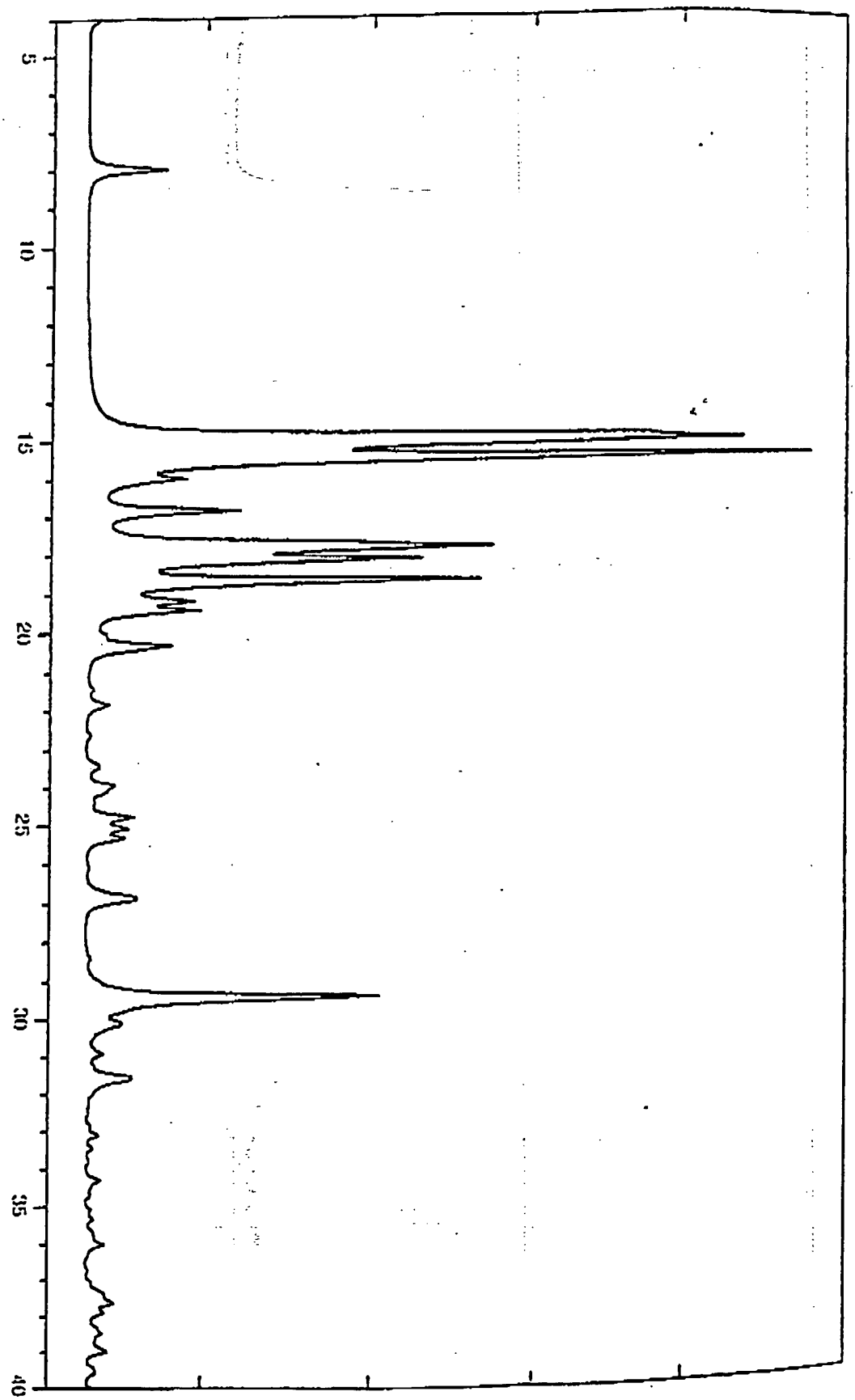


EXHIBIT C



DIEA Form FI XRPD Pattern Calculated from Single Crystal Data

EXHIBIT D

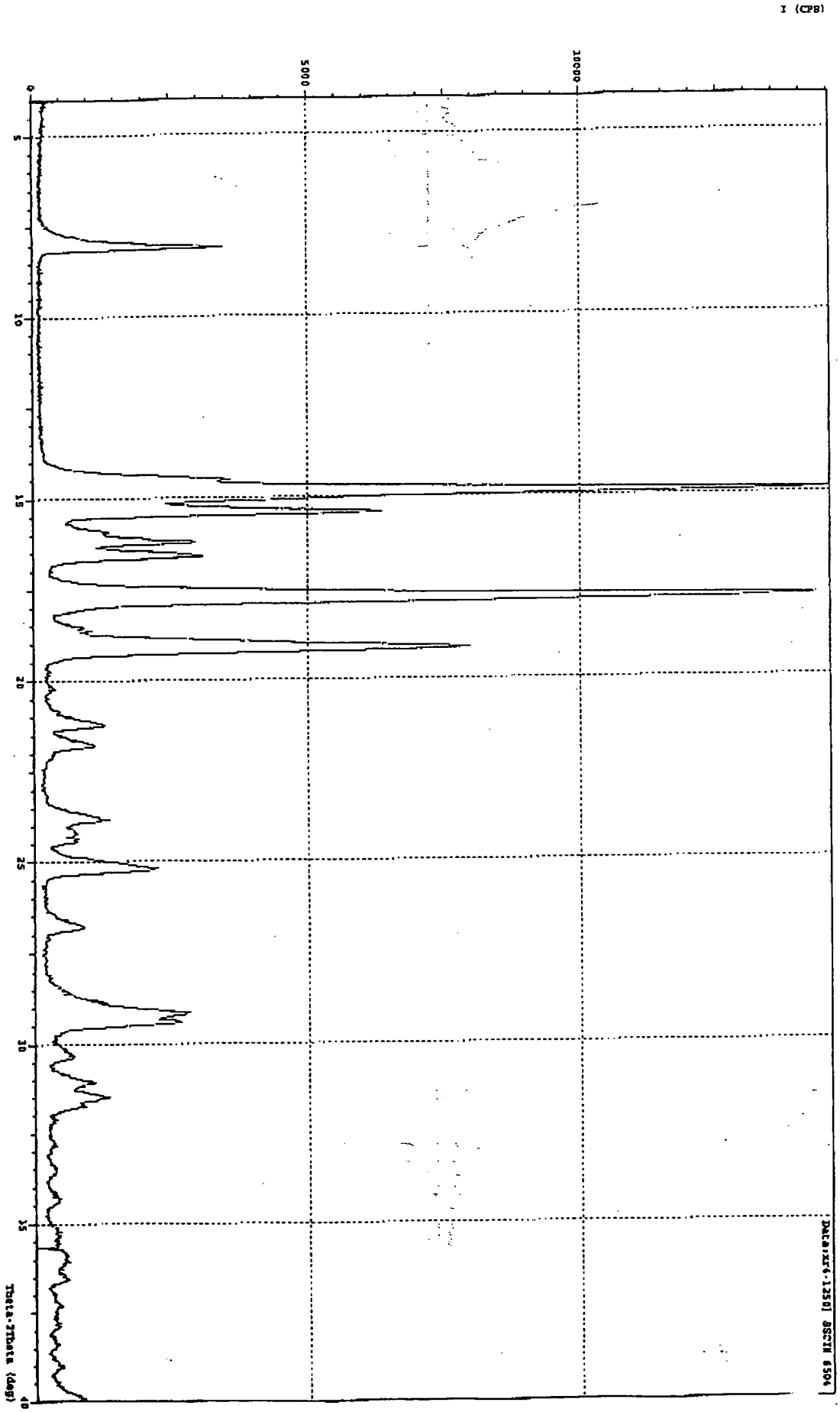

I (CPS)
5000
10000
0
5
10
15
20
25
30
35
40
Theta-2Theta (deg)
DATA:ZSY4-1250 BSCIN 6504

EXHIBIT E

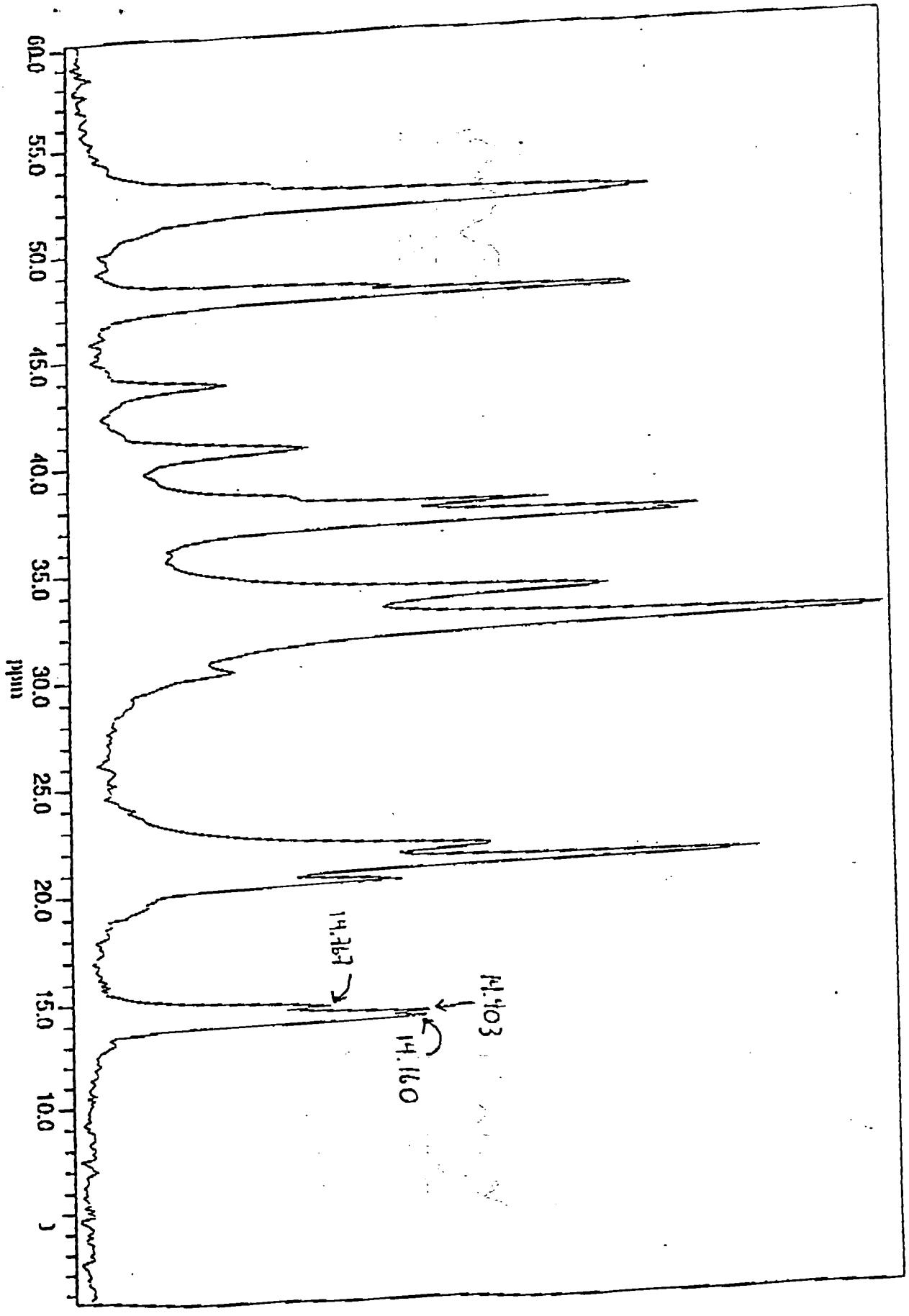

60.0
55.0
50.0
45.0
40.0
35.0
30.0
25.0
20.0
15.0
10.0
min
14.267
14.403
14.160

EXHIBIT F

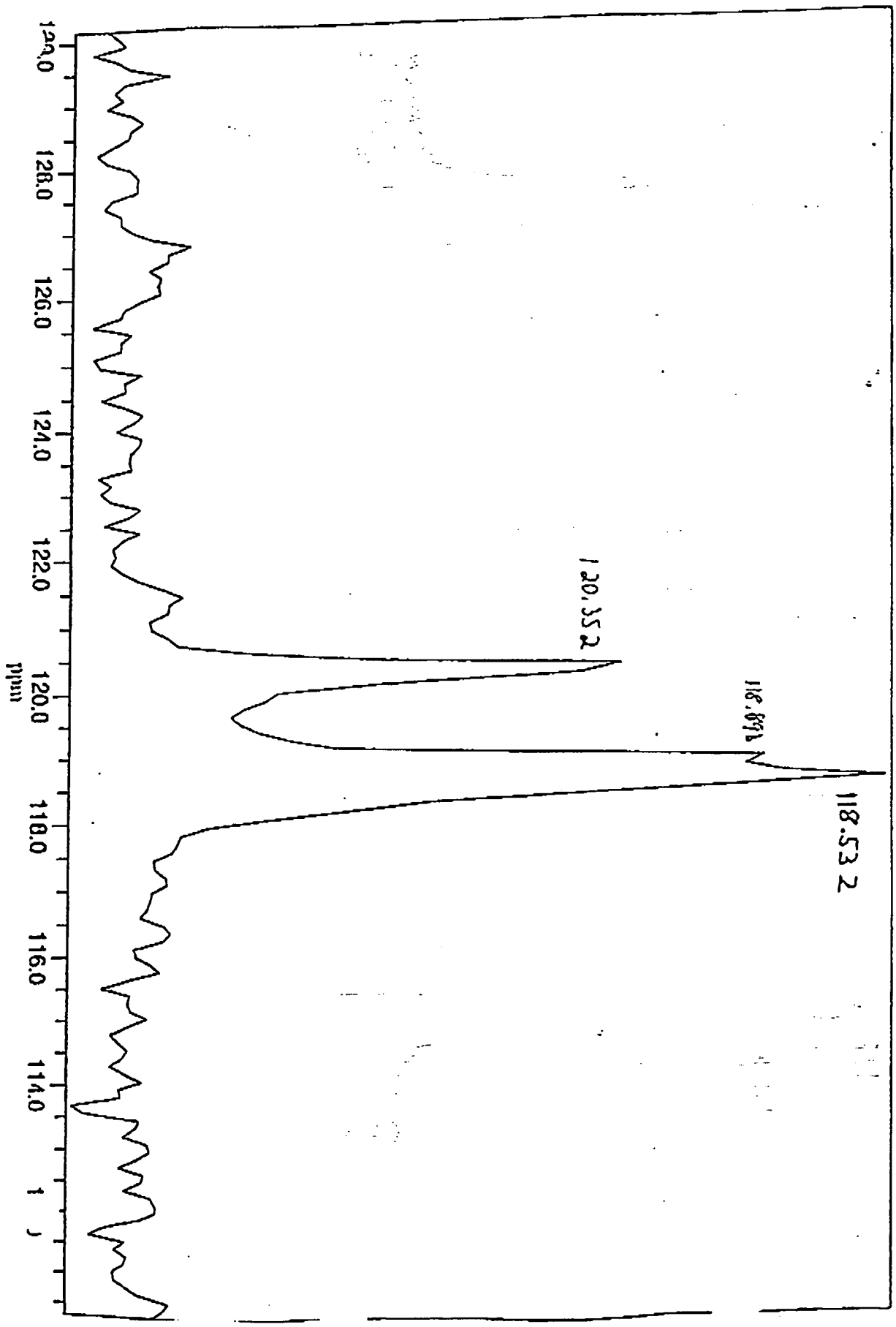

130.0
128.0
126.0
124.0
122.0
120.0
118.0
116.0
114.0
ppm
120.35 2
118.69 1
118.53 2

EXHIBIT G

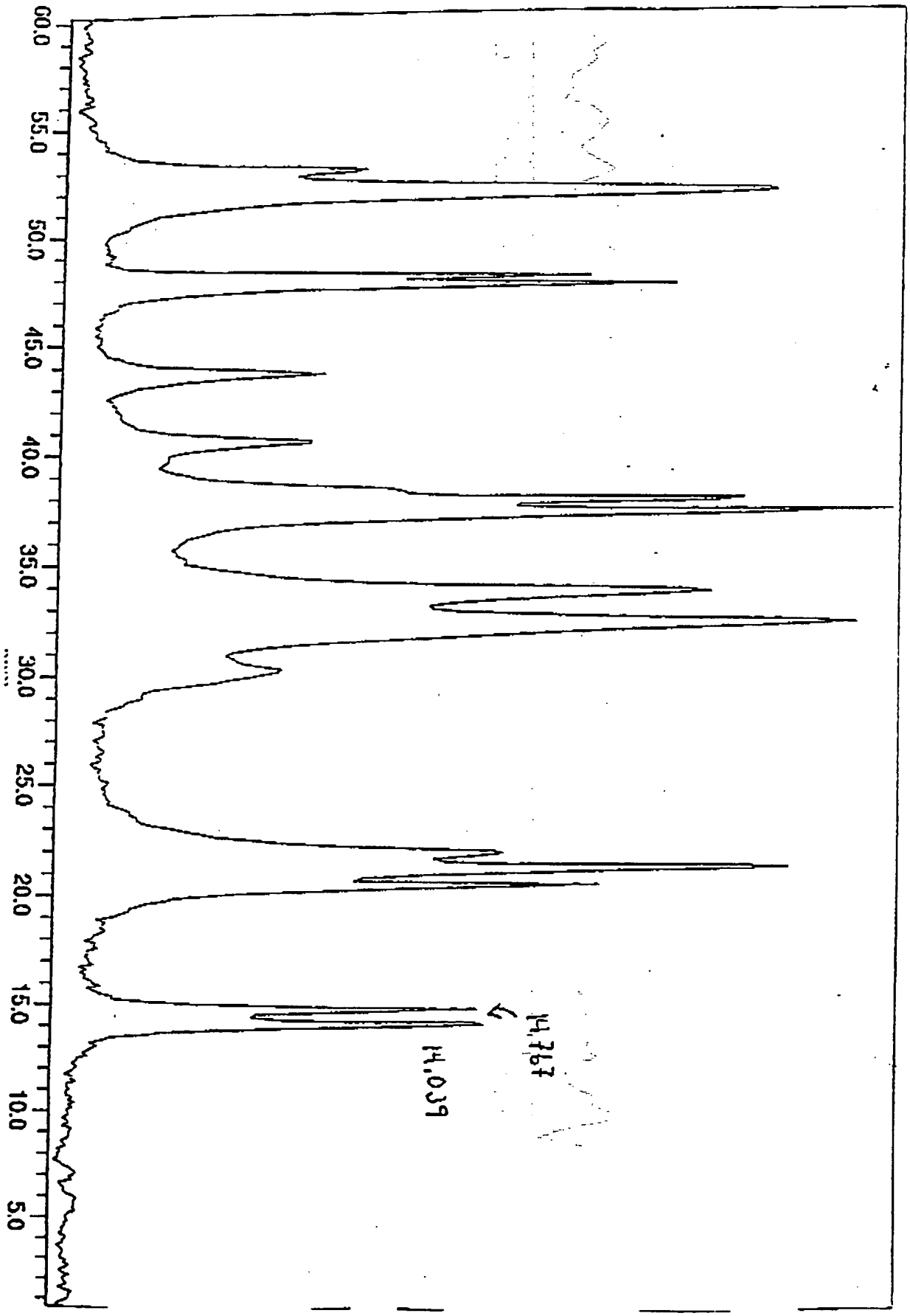
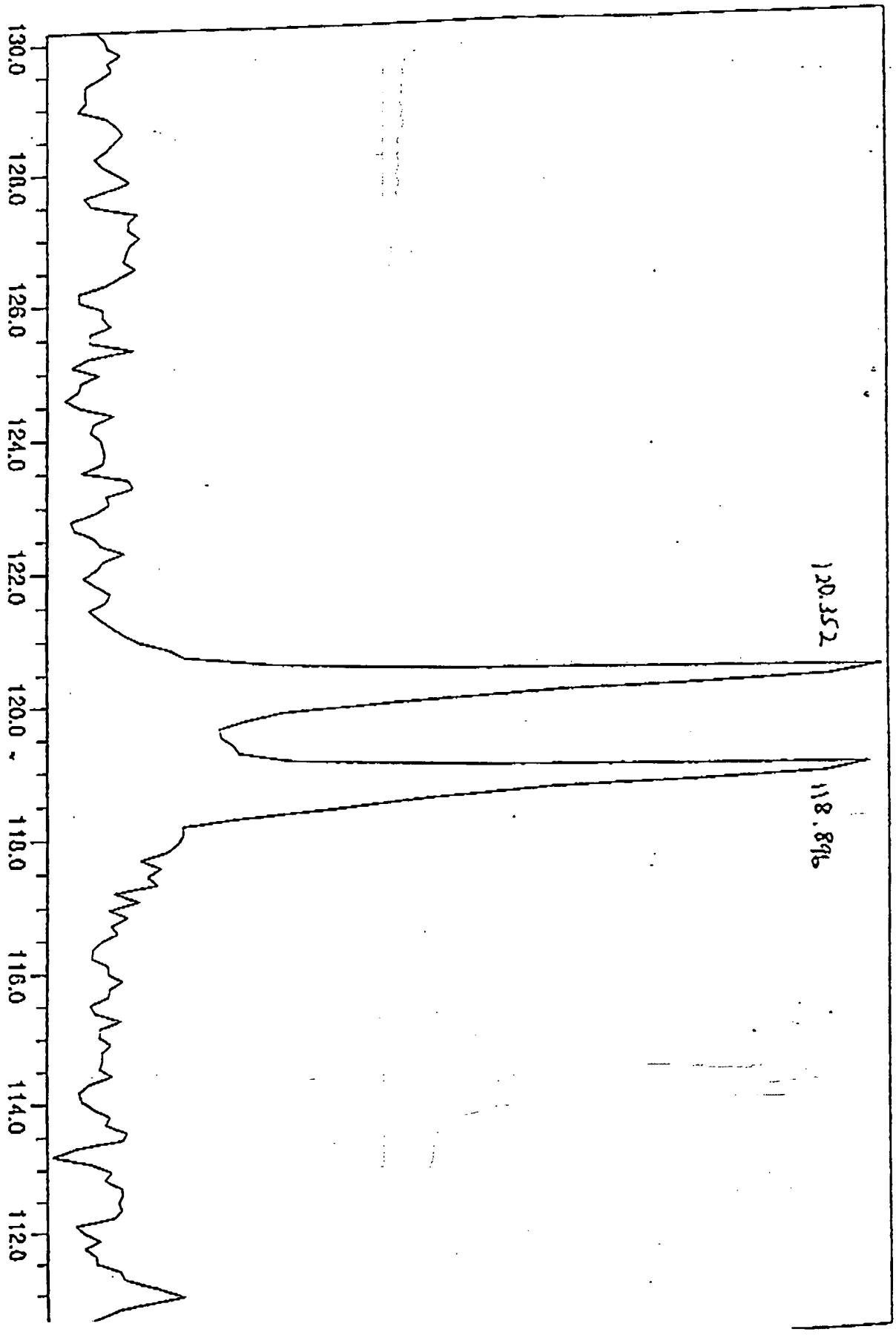


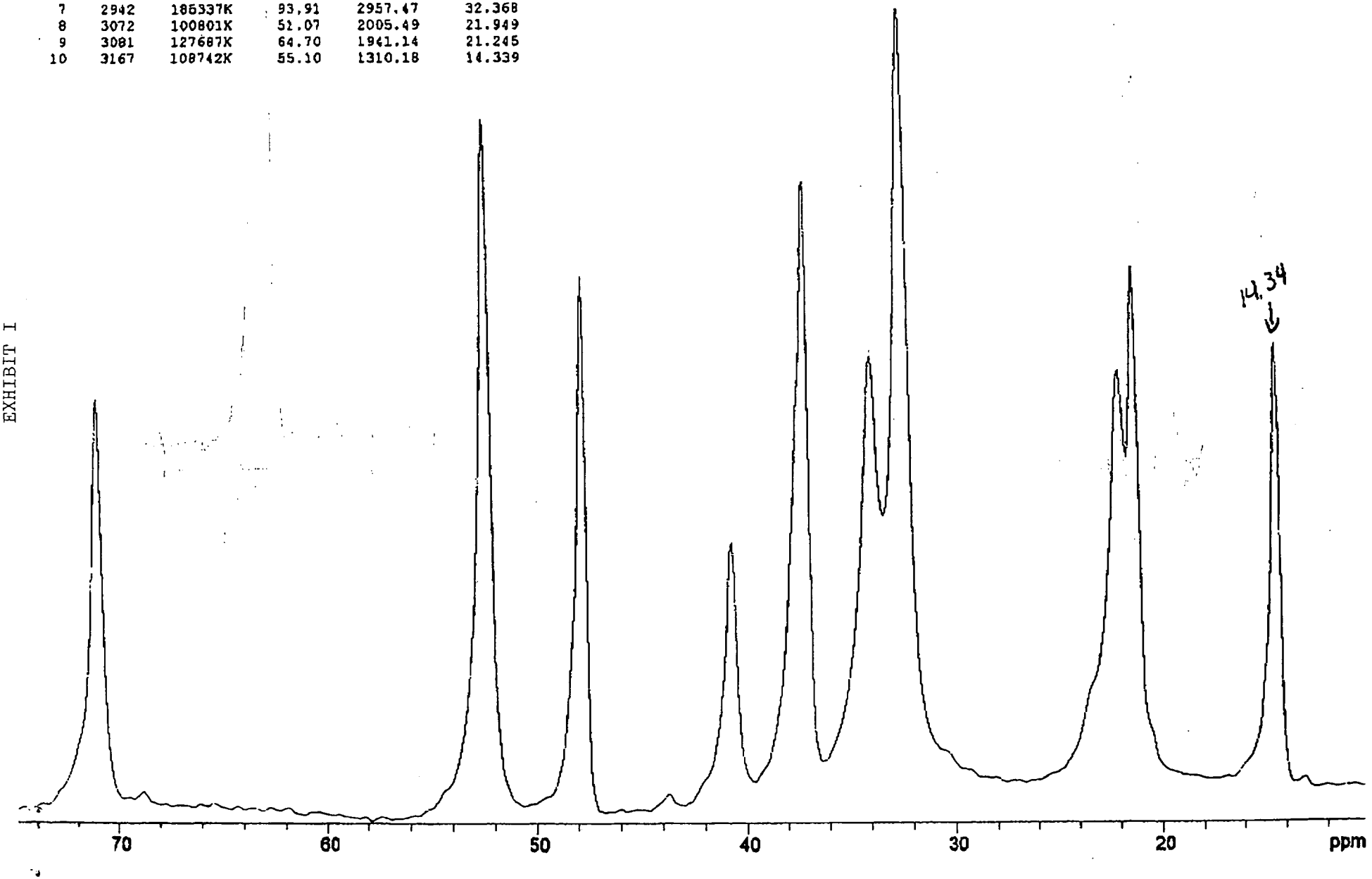
EXHIBIT H


130.0
128.0
126.0
124.0
122.0
120.0
118.0
116.0
114.0
112.0
ppm
120.352
118.896

Interpolated Peak Listing

PEAK	POINT	HEIGHT	REL. HT	HZ	PPM
1	2462	94799K	48.03	6479.82	70.919
2	2693	159969K	81.05	4788.41	52.407
3	2751	124609K	63.14	4362.72	47.748
4	2839	61577K	31.20	3714.77	40.657
5	2884	146003K	73.98	3382.45	37.019
6	2924	104233K	52.81	3089.76	33.816
7	2942	185337K	93.91	2957.47	32.368
8	3072	100801K	51.07	2005.49	21.949
9	3081	127687K	64.70	1941.14	21.245
10	3167	108742K	55.10	1310.18	14.339

EXHIBIT I



Interpolated Peak Listing

PEAK	POINT	HEIGHT	REL. HT	HZ	PPM
1	1562	27363K	13.71	13067.47	143.018
2	1763	8407K	4.21	11600.53	126.963
3	1868	42575K	21.33	10825.71	118.483
4	2163	21628K	10.84	8737.65	95.630

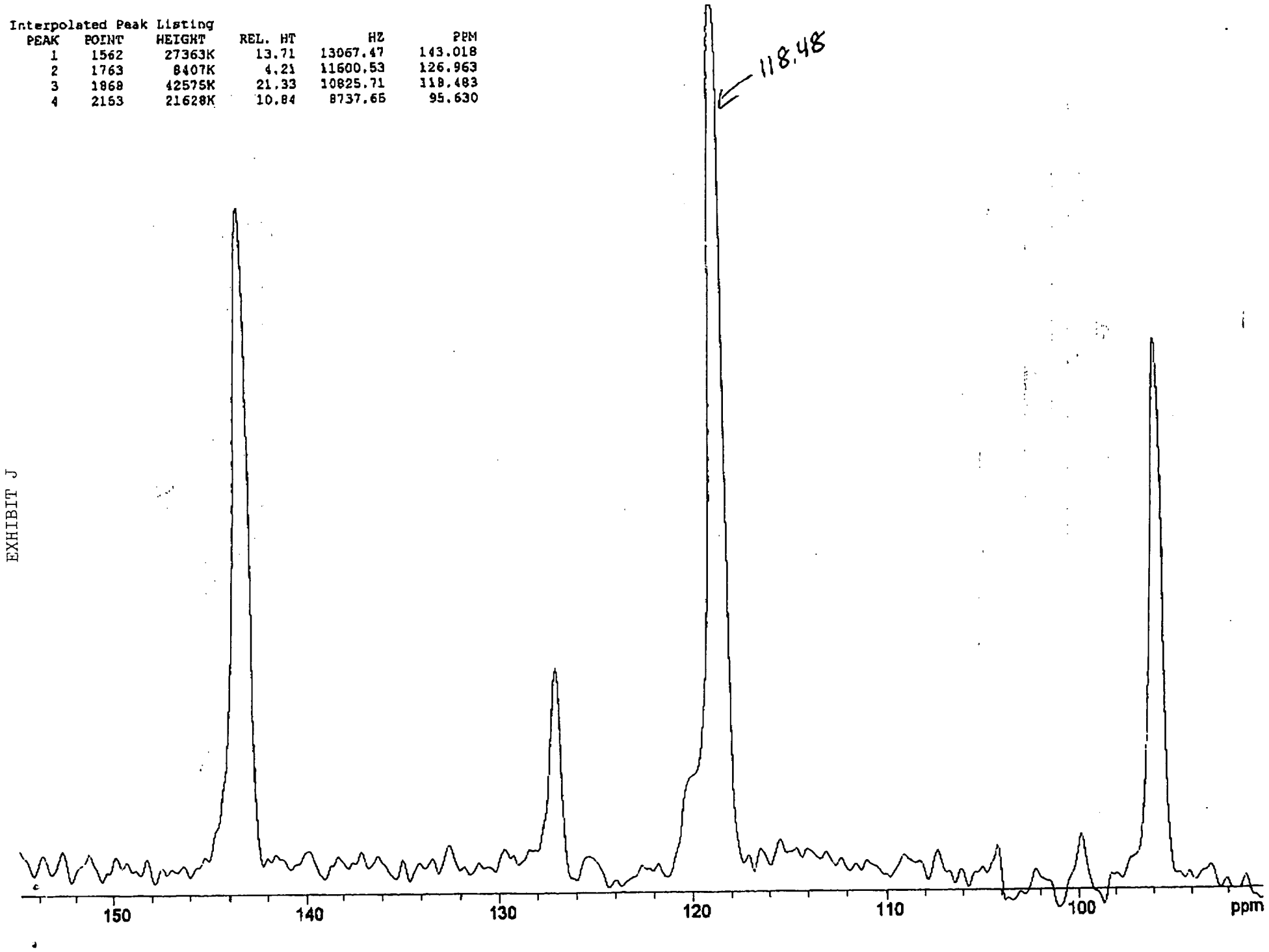


EXHIBIT J

G. PATRICK STAHLY, Ph.D.
SSCI, Inc.
3065 Kent Ave.
West Lafayette, IN 47906
phone: 765-463-0112 fax: 765-497-2649 e-mail: gpstahly@ssci-inc.com

SUMMARY

Senior industrial scientist with record of expertise and creative problem solving in the specialty chemical and pharmaceutical industries. Proven laboratory, organizational, communication, supervisory, and innovation skills. Experienced in chemical synthesis, solid-state chemistry, pharmaceutical preformulation, FDA regulatory requirements, engineering principles, manufacturing demands, economics, and patent law. Demonstrated proficiency from idea conception through commercialization.

POSITIONS HELD

SSCI, Inc., West Lafayette, IN

Chief Operating Officer	1997 – present
Vice President for Research and Development	1995 – present

Albemarle (previously Ethyl) Corporation, Baton Rouge, LA

Senior R&D Advisor	1992 – 1995
R&D Advisor	1991 – 1992
Associate-New Product Development and Manager-R&D	1988 – 1991
Research Chemist, Senior Research Chemist, and Senior Research Specialist	1980 – 1988

EDUCATION

Ph.D., Organic Chemistry, University of Maryland, College Park, MD	1979
B.S., Chemistry, University of Maryland, College Park, MD	1974

PUBLICATIONS

Inventor of 40 U. S. patents
Author of 27 technical publications

AFFILIATIONS

American Chemical Society	1975 – present
American Association of Pharmaceutical Scientists	1996 – present
Purdue University, Adjunct Professor in the Department of Industrial and Physical Pharmacy	1995 – present
Topic Editor for the ACS journal *Crystal Growth & Design*	2000 – present

SELECTED ACCOMPISHMENTS

SSCI, Inc., West Lafayette, IN

- In six years expanded SSCI from 1 full-time employee to 60 full-time employees, increasing annual revenue by 2500% from 1996 to 2001. Revenue in 2001 was about $9 M.
- Company leader responsible for all aspects of growth, including staffing, systems design and implementation (project tracking, GMP, LAN, etc), client identification and development, technical output, and R&D program development.
- Initiated and implemented an R&D program which has generated patent-pending technologies.

Albemarle (previously Ethyl) Corporation, Baton Rouge, LA

- Technical group leader responsible for technical leadership, staffing, goal setting, performance evaluation, and safety performance.
- Led a Manufacturing Technology Team that achieved cost reductions and quality improvements for several commercial products.
- Invented an optical purification method that reduced by $10 million the capital cost of manufacturing a commercial chiral product.
- Created a novel, single-crystal x-ray method to design high-efficiency resolving agents. Obtained funding by winning an internal grant, and successfully invented new agents.
- Instituted and supervised basic research programs in core technology areas of organometallic catalysis and flame retardance.
- Established, coordinated, and administered financing of joint research programs with six academic institutions.
- Evaluated market and technical feasibility of the corporation's proposed research projects. Completed market research studies on top candidates.
- Originated and carried out exploratory research leading to new, patented methods for:
  - Synthesis of several bulk pharmaceuticals.
  - Alkylation of nitroaromatics (used at pilot plant scale).
  - Reduced-waste synthesis of unsymmetrical biphenyls.
  - Syntheses of monomers for specialty polymers.
  - Difluoromethylation of carbonyl compounds.
  - Trifluoromethylation of aromatics.
- Invented a series of perfluoroalkylated profen drugs designed to have enhanced lipid solubility.

G. PATRICK STAHLY, Ph.D.

PUBLICATIONS

1. Jarvis, B.B.; Stahly, G.P.; Curtis, C.R. *Cancer Treat. Rep.* **1978**, *62*, 1585. Antitumor Activity of Fungal Metabolites: Verrucarin Beta-9,10-epoxides.
2. Jarvis, B.B.; Stahly, G.P.; Ammon, H.L. *Tetrahedron Lett.* **1978**, 3781. A Novel New Heterocycle from the Reaction of Azide Ion with 2,3-Diphenylthiirene 1,1-Dioxide.
3. Jarvis, B.B.; Stahly, G.P.; Pavanasasivam, G.; Mazzola, E.P. *J. Antibiotics* **1980**, *33*, 256. Structure of Roridin J, A New Macrocyclic Trichothecene from *Myrothecium Verrucaria*.
4. Jarvis, B.B.; Midiwo, J.O.; Stahly, G.P.; Pavanasasivam, G.; Mazzola, E.P. *Tetrahedron Lett.* **1980**, 787. Trichodermadiene: A New Novel Trichothecene.
5. Stahly, G.P.; Ammon, H.L.; Jarvis, B.B. *Acta Cryst.* **1980**, *B36*, 2159. The Structure of 4-[(E)-1,2-Diphenylvinyl]-2,6-diphenyl-1,3,4,5-thiatriazine 1,1-Dioxide.
6. Jarvis, B.B.; Stahly, G.P.; Pavanasasivam, G.; Mazzola, E.P. *J. Med. Chem.* **1980**, *23*, 1054. Antileukemic Compounds Derived from the Chemical Modification of Macrocyclic Trichothecenes. 1. Derivatives of Verrucarin A.
7. Jarvis B.B.; Stahly, G.P. *J. Org. Chem.* **1980**, *45*, 2604. Reactions of 2,3-Diphenylthiirene 1,1-Dioxide with Nucleophiles.
8. Jarvis, B.B.; Pavanasasivam, G.; Holmlund, C.E.; DeSilva, T.; Stahly, G.P.; Mazzola, E.P. *J. Am. Chem. Soc.* **1981**, *103*, 472. Biosynthetic Intermediates to the Macrocyclic Trichothecenes.
9. Jarvis, B.B.; Stahly, G.P.; Pavanasasivam, G.; Midiwo, J.O.; DeSilva, T.; Holmlund, C.E.; Mazzola, E.P.; Geoghegan, R.F. *J. Org. Chem.* **1982**, *47*, 1117. Isolation and Characterization of the Trichoverroids and New Roridins and Verrucarins.
10. Stahly, G.P.; Marlett, E.M.; Nelson, G.E. *J. Org. Chem.* **1983**, *48*, 4423. Selective Hydrolysis-Decarboxylation of Ethyl 1,4-Dimethyl-3-(ethoxycarbonyl)-1H-pyrrole-2-acetate.
11. Stahly, G.P.; Stahly, B.C.; Lilje, K.C. *J. Org. Chem.* **1984**, *49*, 578. Synthesis of 2-(4-Nitroaryl)propionate Esters.
12. Stahly, G.P. *J. Org. Chem.* **1985**, *50*, 3091. Synthesis of Unsymmetrical Biphenyls by Reaction of Nitroarenes with Phenols.
13. Stahly, G.P. *Synth. Commun.* **1987**, *17*, 1053. A Diels-Alder Approach to 4,4'-Thiobis(phthalic acid) Derivatives.
14. Stahly, G.P.; Stahly, B.C.; Maloney, J.R. *J. Org. Chem.* **1988**, *53*, 690. Base-Induced Reactions of Polynitroarenes with Methyl 2-Chloropropionate.
15. Stahly, G.P. *J. Fluorine Chem.* **1989**, *43*, 53. Nucleophilic Addition of Difluoromethyl Phenyl Sulfone to Aldehydes and Various Transformations of the Resulting Alcohols.
16. Stahly, G.P.; Bell, D.R. *J. Org. Chem.* **1989**, *54*, 2873. A New Method for Synthesis of Trifluoromethyl-Substituted Phenols and Anilines.
17. Stahly, G.P. *J. Fluorine Chem.* **1989**, *45*, 431. Trifluoromethylation of 1,3,5-Trinitrobenzene.
18. Stahly, G.P.; Jackson, A. *J. Org. Chem.* **1991**, *56*, 5472. Synthesis of 2-(Perfluoroalkylphenyl)propionic Acids.
19. Stahly, G.P. *Today's Chemist at Work* **1993**, *2*, 28. TLC: An Often Overlooked Tool Giving Speed and Convenience at Low Cost.

G. PATRICK STAHLY, Ph.D.

PUBLICATIONS

20. Manimaran, T.; Wu, T-C.; Klobucar, W.D.; Kolich, C.H.; Stahly, G.P.; Fronczek, F.R.; Watkins, S.E. *Organometallics* **1993**, *12*, 1467. In-situ Generation of Ruthenium-Chiral Phosphine Complexes and Their Use in Asymmetric Hydrogenation.
21. Manimaran, T.; Stahly, G.P. *Tetrahedron: Asymmetry* **1993**, *4*, 1949. Optical Purification of Profen Drugs.
22. Wu, F. J.; Stahly, G. P.; Fronczek, F. R.; Watkins, S. F. *Acta Crystallogr., Sect. C*, **1995**, 18. The Structure of 1,4,7-Tri-*n*-butyl-1,4,7-triazacyclononanechromium Trichloride.
23. Stahly, G.P.; Starrett, R.M. in *Chirality in Industry II*; Collins, A. N.; Sheldrake, G. N.; Crosby, J., Eds.; Wiley & Sons: New York, 1997, Chapter 3. Production Methods for Chiral Non-steroidal Anti-inflammatory Profen Drugs.
24. Stahly, G.P.; McKenzie, A.T.; Andres, M.C.; Russell, C.A.; Byrn, S.R.; Johnson, P. *J. Pharm. Sci.* **1997**, *86*, 970. Determination of the Optical Purity of Ibuprofen Using X-ray Powder Diffraction.
25. Stahly, G.P.; Byrn, S.R. in *Molecular Modeling Applications in Crystallization*; Myerson, A.S., Ed.; Cambridge University Press: New York, 1999, Chapter 6. The Solid-State Structure of Chiral Organic Pharmaceuticals.
26. He, X.; Stowell, J.G.; Morris, K.R.; Pfeiffer, R.R.; Li, H.; Stahly, G.P.; Byrn, S.R. *Crystal Growth & Design* **2001**, *1*, 305. Stabilization of a Metastable Polymorph of 4-Methyl-1,2-nitroacetanilide by Isomorphic Additives.
27. Newman, A.W.; Stahly, G.P. in *Handbook of Pharmaceutical Analysis*; Ohannesian, L.; Streeter, A.J., Eds.; Drugs and the Pharmaceutical Sciences Series 117; Marcel Dekker: New York, 2001, Chapter 1. Form Selection of Pharmaceutical Compounds.